

OVERVIEW OF CLINICAL STUDIES

The primary efficacy data supporting the proposed indication for the treatment of chemotherapy-refractory patients with low grade and follicular NHL, with or without transformation are derived from Study RIT-II-004. The primary efficacy data supporting the indication for the treatment of Rituxan-refractory patients with low grade and follicular NHL, with or without transformation, are derived from Study CP-97-012. Three additional studies (RIT-I-000, RIT-II-001, and RIT-II-002) provide supportive anti-tumor activity data for the proposed indications.

Safety information relevant to single agent use of Iodine I-131 tositumomab in this patient population were obtained from the five efficacy/activity studies, the interim results of an additional study (RIT-II-003) conducted as an exploratory, Phase 2 study of initial treatment in patients with low grade, follicular NHL. Additional, limited safety data are provided from the expanded access experience under Protocol CP-98-020 and supplement by data provided to the sponsor from --- sponsor-investigator INDs for the treatment of individual patients.

INDIVIDUAL CLINICAL STUDY RESULTS

STUDY RIT-II-004

Title: Multicenter, Pivotal Phase 3 Study of Iodine I 131 tositumomab (Murine) Radioimmunotherapy for Chemotherapy-Refractory Low-Grade B-Cell Lymphomas and Low-Grade Lymphomas that Have Transformed to Higher Grade Histologies.

Design: A multicenter, historically-controlled, single-arm trial in patients with chemotherapy-refractory low grade or follicular NHL, with or without transformation.

Study opened- November 22, 1996

Study closed to accrual - March 6, 1998

Data cut-off- January 28, 2002

Study Sites

- Christie Hospital (UK)
- Cornell Medical Center
- Dana-Farber Cancer Institute
- Georgetown University
- Kaiser Permanente Medical Center
- Memorial Sloan-Kettering Cancer Center
- Rush-Presbyterian-St. Luke's Medical Center
- St. Bartholomew's Hospital (UK)
- Stanford University Medical Center
- University of Alabama at Birmingham
- University of Michigan Medical Center
- University of Nebraska Medical Center
- University of Washington
- Yale University School of Medicine

Specific Aims and Objectives (original protocol)

1. To establish the response rate, response duration, time to progression, time to treatment failure and survival after treatment with iodine I-131 tositumomab Radioimmunotherapy (RIT) in patients with chemotherapy-refractory low-grade or transformed non-Hodgkin's lymphoma
2. To compare these endpoints to the patient's previous chemotherapy outcome
3. To assess the safety of iodine I-131 tositumomab RIT
4. To assess the quality of life of treated patients using the ----- validated questionnaire.

Eligibility criteria (original protocol)

Inclusion Criteria

1. Histologically confirmed diagnosis of CD20 positive low-grade or transformed low-grade non-Hodgkin's lymphoma.
2. Treatment with at least two cycles of a qualifying chemotherapy regimen (6 weeks of single agent therapy) (see below), with failure to achieve an objective response, or relapse/progression within 6 months after completion of the last qualifying chemotherapy (LQC) regimen. Patients must have objective evidence of relapse or failure to respond.
3. Karnofsky Performance Status $\geq 60\%$; anticipated survival of 3 months.
4. Absolute granulocyte count $> 1500/\text{mm}^3$ and a platelet count $> 100,000/\text{mm}^3$.
5. Adequate renal (creatinine $< 2.0 \text{ mg/dL}$) and hepatic function (bilirubin $< 2.0 \text{ mg/dL}$).
6. Bidimensionally measurable disease or evaluable disease.
7. Copies of original medical notes and radiographic studies documenting the chemotherapy drugs, number of courses and dates of their LQC, response to the LQC and, for responders, the date of disease progression.

Exclusion Criteria

1. An average of $> 25\%$ of the intratrabecular marrow space involved with lymphoma.
2. Prior hematopoietic stem cell transplant.
3. Active obstructive hydronephrosis.
4. Pregnant or nursing females.
5. Disease progression within one year, arising in a field previously irradiated with $> 3500 \text{ cGy}$.
6. Concurrent treatment with any other anti-cancer drugs or biologics.

Qualifying chemotherapy regimens

Original protocol

- Low grade NHL: CVP, COP-Bleo, CP, cytoxan, chlorambucil, fludarabine
- Intermediate grade NHL: C-MOPP, BACOP, CHOP, CHOP-Bleo, ProMACE-MOPP, CHOP-Bleo + alpha interferon, COMLA, MINE, ESHAP, DHAP, EPOCH, CEPP, ProMACE-CytoBOM, ICE, COP-BLAM, CNOP, FND, MACOP-B, m-BACOD

Added in amendment 1 (-----)

- Intermediate grade NHL: VAPEC-B, IM-VP16

Added in amendment 2 (-----)

- CF, cladribine

Monitoring Plan (Original Protocol)

1. Baseline (Within 2 weeks of Enrollment)

History and Physical with Karnofsky Status; Lab – CBC, Serum Chemistry (Creatinine, Total Bilirubin, Na K, Cl, Bun, LDH, Urinalysis Thyroid functions, HAMA); Tumor Staging consisting of Bone Marrow within 42 days of entry; CT and other radiographs as needed of the chest, abdomen, pelvis within 28 days of entry

2. Days 0; Day 2, 3, or 4; and Day 7
Whole body biodistribution, Whole body dosimetry, and calculation of therapeutic dose
3. Treatment phase
CBC weekly for weeks 3-9, 13 & 25; Serum Chemistry weeks 3, 7, 13 & 25; tumor restaging (physical examination, radiologic studies, and bone marrow biopsy [if positive at baseline]) weeks 7, 13, and 25; HAMA weeks 7 & 25
4. Follow-up (Every 13 weeks up to 2 years or until discontinuation)
History and Physical with Karnofsky Status; CBC, Serum Chemistry, HAMA; Tumor restaging studies including radiologic evaluations and bone marrow biopsy
5. Long-term follow-up: Disease status and vital status every 6 months

Treatment Plan

The treatment consisted of two intravenous infusions; an initial dosimetric infusion followed in 7 to 14 days by a therapeutic infusion.

- The first day of the dosimetric phase was designated as study day 0. The dosimetric infusion contained 450 mg of tositumomab infused over 70 minutes (includes a 10 minute flush) immediately followed by 5 mCi (35 mg) of iodine I-131 tositumomab iodine infused over 30 minutes (includes a 10 minute flush).
- Seven to 14 days later the therapeutic dose consisting of 450 mg of tositumomab was infused over 70 minutes (includes a 10 minute flush) immediately followed by the patient –specific mCi activity (35 mg) of iodine I-131 tositumomab calculated to deliver a total body dose of 75 cGy and infused over thirty minutes. The calculation of the patient specific dose was base on the information obtained from the dosimetric infusion and is detailed in the protocol.
- The therapeutic dose was calculated to deliver 75 cGy TBD in patients with platelet counts $\geq 150,000/\text{cu mm}$. Patients with platelet counts between 100,001 and 150,000/cu mm were administered a therapeutic dose calculated to deliver 65 cGy TBD. Obese patients were dosed based upon 137% of their lean body mass.

Dose Modifications

- Obesity
Excessively obese patients (defined as patients weighing more than 137% of the calculated lean body mass) the calculations to determine the iodine I-131 tositumomab activity will be performed using an upper limit of mass (maximum effective mass) based upon height and gender (Table for determination of max effective mass included as Appendix 2 to the protocol).
- Baseline Thrombocytopenia
The administered dose for patients with platelet counts between 100,001 and 150,000/cu mm will be adjusted to deliver an estimated activity of 65cGy TBD. An additional adjustment for obesity may be performed, if indicated.
- Toxicity
 - The infusion rate was to be decreased by 50% for fever of $38.5\text{--}38.9^{\circ}\text{C}$, mild to moderate rigors, mild to moderate mucosal congestion/edema, or 30-49% drop in systolic blood pressure

- The infusion was to be stopped until resolution of toxicity and then resumed at 25-50% of the original infusion rate for fever >39°C, severe rigors, severe mucosal congestion/edema, or 50% decrease in systolic blood pressure.
- Patients who have not received at least 3 doses of SSKI, 3 doses of Lugol's solution, or 130 mg of potassium iodide at least 24 hours prior to the dosimetric dose, may not receive the dosimetric dose
- Patients who are seropositive for HAMA at day 5 may not receive the therapeutic infusion.

Concomitant Medications

- All patients were required to receive either Lugol's solution or potassium iodide tablets, beginning 24 hours before the dosimetric dose and continuing until 14 days after the last infusion of radiolabeled antibody.
- Thirty minutes prior to both the dosimetric dose and the therapeutic dose, all patients were premedicated with acetaminophen 650 mg p.o. and diphenhydramine 50 mg p.o.

Analytic Plan (Original Protocol)

Primary and Secondary Endpoints

The primary efficacy endpoint for this study will be the Overall Response Rate and duration established on this study.

Secondary efficacy endpoint analyses for this study will be survival, time-to-progression, time-to-treatment failure established on this study. Quality of life and safety analyses will also be included as secondary endpoint analyses. In addition, the response rate, response duration, time to progression and time to treatment failure will be compared with the patient's last qualifying chemotherapy regimen.

Statistical Considerations

The proposed sample size of 60 patients was selected to enable response rates to be estimated with a maximum standard error of 0.065. The protocol stated that any patient who is enrolled but does not complete both the trace and therapeutic dose of Anti-B1, will be replaced so that a total of 60 radioimmunotherapy treated patients will be enrolled. Projected completion of accrual was September 1997.

Establishing of Response Rate, Best Response Rate and Duration Measures

Estimates of the rates of response, complete response and overall response (complete, clinical complete and partial), will be estimated from the study response rates. All acquired data will be analyzed by intention-to-treat. Point estimates and two-sided 95% confidence intervals will be calculated. One-sided 95% confidence intervals for minimum response rates will also be calculated. Mean and median duration response, time-to-progression, time-to-treatment failure, and survival will be calculated. If the study evaluation is performed before all data have reached their respective endpoints, right censored data for duration estimates will be treated as independent censoring and Kaplan-Meier survival estimates will be employed. Time-to-progression analyses will treat patients' withdrawals and interventions for reasons other than progression or death as independent censoring. Subgroup analyses by number of previous therapies, time from diagnosis, histology, and previous response will be performed.

Efficacy Analyses: Patients As Their Own Control

Although the eligibility criteria restrict the study to patients who completed their previous qualify chemotherapy regimen so that the appropriate comparison is based on patients who complete treatment, all acquired data will be analyzed by intention-to-treat methods. Two-sided paired-sample tests of equivalency of the response rates following RIT with the last previous qualifying chemotherapy response will be performed at the 5% level. Paired t-test and non-parametric Wilcoxon signed rank tests comparing the duration of response, time-to-progression, and time-to-treatment failure will be performed. If right-censoring is present, pair-matched censored survival tests will be performed. No stratification is present in the study as the patients as their own control performs this function. Subgroup analyses by number of previous therapies, time from diagnosis, histology, and previous response will be performed.

Revised, Final Analytic Plan

The primary endpoint of the study was a comparison of the number of patients having a longer duration of response (i.e., >30 days longer) after iodine I 131 tositumomab therapy compared to the number of patients having a longer duration of response after their LQC regimen. For the purposes of the primary efficacy endpoint, efficacy outcomes after the LQC and iodine I 131 tositumomab therapies were assessed by the MIRROR Panel. Secondary efficacy endpoints were response rate, complete response rate, and time to progression or death.

The original sample size of 60 patients is adequate to detect a difference of 25% in the proportion of patients experiencing a longer duration of response (greater than 30 days) when treated with iodine I 131 tositumomab therapy compared to the proportion of patients experiencing a longer duration of response (greater than 30 days) to the LQC.

There are two dichotomous treatment outcomes that are assessed in this analysis

- Durations equivalent- defined as ≤ 30 days difference in response durations to Iodine I-131 tositumomab and to prior chemotherapy for an individual patients
- Durations non-equivalent- defined as > 30 days difference in the durations of response to Iodine I-131 tositumomab and to prior chemotherapy.

Only the non-equivalent cases contribute to the test statistic in this approach. The null hypothesis is that the durations of response are the following the most recent chemotherapy regimen and following Iodine-131 Anti-B1 Antibody therapy.

Statistical Test Method - McNemar's test

The assumptions used in this trial were that the expected proportion of patients responding to therapy decreases with each successive therapy. Under this assumption, it is expected that the proportion of patients responding to Iodine-131 Anti-B1 Antibody would be smaller than the proportion of patients who responded to the most recent, preceding chemotherapeutic regimen.

A test incorporating the expected decrease in response was named a modified McNemar's test and, under the null hypothesis, the McNemar's test statistic was expected to equal 0.375. This corresponds to 75% of the 0.5 expected under the test,

which ignores the order of therapies described in the previous paragraph. A one-sided exact binomial test was used.

Table M
Outcomes for McNemar's Test

		Prior Chemotherapy	
		No Response	Response
Iodine-131 Anti-B1 Antibody	No Response	A	B
	Response	C	D

The McNemar's test is a test of the equality of the probability of each of these two groups. The response rate on the comparative chemotherapy is equal to that on Iodine-131 Anti-B1 Antibody if the number of patients in Group B equals the number of patients in Group C. McNemar's test statistic equals the proportion of patients in Group C of the patients in Group B or Group C. Under the null hypothesis, this equals 0.5.

Efficacy analyses were to be conducted on a modified intent-to-treat basis, i.e., the analyses of efficacy include all patients who received any portion of the study drug including only the dosimetric dose.

MIRROR Panel

The MIRROR Panel was composed of two radiologists and two oncologists. All were board certified in their respective disciplines. The panel reviewed both patient radiographs and patient medical notes, while masked to the investigators' assessments of response. Efficacy endpoints include response rate, complete response rate, duration of response and time to progression based on the MIRROR Panel independent review assessment. The independent review process was coordinated by an independent CRO. The representative from the CRO facilitated the review process and ensured appropriate masking of the data and completion of the CRFs.

Amendments to the protocol and dates of amendment

Amendment 1- -----

- Expanded aims and objectives of the study defined the primary endpoint (overall response rate) and expanded the secondary endpoints to include 3 types of response rates (Best Response [regardless of durability], Response, and Prolonged Response), duration of unmaintained response, TTP, TTF, and survival. The results for each of these endpoints following Iodine I-131 tositumomab would be compared to that observed following the LQC, except for survival.
- Inclusion criteria modified to permit CD20 expression using any commercial antibody similar to the ---- or anti-B1 antibody; to allow for a limited exposure to treatment between the LQC and study entry, if the patient progressed on or after the intervening therapy and was enrolled within 6 months of completion of the LQC; added LDH <500 IU/mL; required that all patients have measurable disease; required patients with intervening chemotherapy to provide radiographic studies documenting baseline, best response, and

Amendment 2 - -----

- Aims and Objectives section revised to add the following "To compare the response rates, duration of responses, and time to treatment failure after 131-Iodine anti-B1 antibody RIT" to the patients previous qualifying chemotherapy outcome."

- Endpoints revised to read as follows: “The primary efficacy endpoint of the study is the comparison of the number of patients having a longer duration of response on Iodine-131 Anti-B1 antibody therapy to the number of patients having a longer duration of response on their last qualifying chemotherapy regimen. Secondary efficacy endpoint analyses are to establish response rates, complete response rates, time-to-progression, time-to-treatment failure, and survival established on this study. The comparison of the response rate and the TTF following RIT with the response rate and the time to treatment failure following the last qualifying chemotherapy regimen are additional secondary endpoint analyses. Quality of life and safety analyses will also be included as secondary endpoint analyses. Survival will be analyzed following RIT only. ”
- Eligibility criteria modified to (1) delete requirement for testing tumor biopsy material for CD20 antigen expression, (2) require that patients must have failed to respond or progressed within 6 months of completion of any additional therapy (after last qualifying therapy but prior to study entry) (3) delete LDH <500 IU/mL and WBC >3500/mm³, (4) adds stated that “at least one lesion must be at least 2 cm diameter” to requirement that patients have bidimensionally measurable disease, (5) changes requirement for baseline radiographic study for evaluation of LQC and any interval, non-qualifying therapy, to be obtained with 10 weeks prior to initiation of that therapy [previously required within 6 weeks prior to therapy] and also requires that medical notes documenting the patient’s course on the LQC must be available, (6) broadens exclusion criteria to exclude patients receiving approved or non-approved anti-cancer drugs or biologics (previously excluded only non-approved drugs) (7) deletes exclusion criterion for patients who have been exposed to non-human monoclonal or polyclonal antibodies [such patients may be enrolled in seronegative for HAMA]
- Correction in of antibody dose administered based on more accurate protein measurement
- Permits multiple use of Anti-B1 vials (i.e., to prepare doses for more than one patient from the same vial)
- Treatment plan modified to require use of an in-line filter for infusion of study drug
- Limits collection of information on concomitant medications to the first 12 weeks of study, unless medication used to treat a drug-related adverse experience
- Revision of patient monitoring schema: (1) Expands follow-up for patients with disease progression. Patients who progress or have been followed without progression for 2 years will be evaluated every 6 months by physical exam and staging studies, evidence of toxicity (particularly pulmonary toxicity) and “thyroid function will be determined periodically”; (2) Adds β 2 microglobulin to baseline and on-study evaluations; (3) Blood sampling for pharmacokinetic analyses to be performed at one study site (-----); (4) States that HAMA assessment may be performed at study sites rather than by a central lab.
- Modifies duration of assessment for serious adverse events from first 12 weeks on study to 12 weeks or administration of alternative therapy for lymphoma, whichever occurs first
- Extensive changes to statistical analysis section, including brief description of the procedures for review of medical records and radiographs to assess response and response duration to LQC and to Iodine I-131 tositumomab.
- Common Toxicity Criteria added as supplemental grading scale
- Modifies criteria for LQC to state that patients must receive at least 2 cycles of combination chemotherapy or 6 weeks of single agent therapy of the LQC, allows addition of agents to single agent and combination regimens or deletion of a drug (that drug or drug in that class) from a combination regimen if patient is known to be intolerant of, or have disease that is refractory to, the drug.

Amendment 3 -----

- Change title from “Phase II/III” to “Phase III”
- Radiolabeled anti-B1 (dosimetric and therapeutic doses) shipped as patient-specific doses from ----- to the study site.
- Definition of measurable disease modified in section of Response criteria to state “measurable lesions are defined as any lesion >2 cm in both perpendicular diameters at baseline.”

- Addition of cladribine to LQC regimens

Amendment 4 -----

- Inclusion criteria modified with regard to documentation of response to last qualifying regimen. Written documentation must be provided from the referring physician (i.e., copies of original medical notes and radiographic reports) specifying the agents in the LQC, the number of course administered, the start and stop dates of LQC, the response to LQC, the date of response to LQC if applicable, and the date that stable or progressive disease. The same written documentation must be provided for any intervening non-qualifying therapy. Written documentation to be submitted to Coulter with the eligibility checklist and prior to enrollment, the documentation will undergo independent review to ensure that it is adequate. In addition, all radiographic studies for assessment of disease status at baseline, at best response (if applicable), and at progressive disease must be supplied to -----
----- for the LQC and any intervening non-qualifying chemotherapy regimen before the patient is enrolled. Evaluations that constitute evidence of disease progression after the last chemotherapy may also be used as the baseline for this study.
- Revision in definition of TTF; treatment failure to include “the decision to seek additional therapy” as an event, in addition to treatment withdrawal, study removal, [disease] progression, alternative therapy for patient’s lymphoma, or death.

Amendment 5 - -----

- Revised study endpoints to specify that (1) the primary efficacy endpoint will be based on response and response duration as assessed by the independent review panel; (2) all efficacy analyses will be performed using both Investigator-assessed and masked, independent review panel-assessed data.
- Modifies study population to state that any patient who is “determined to be HAMA-positive at baseline according to the validated, centralized HAMA assay will be replaced so that a total of 60 HAMA-negative patients who have received radioimmunotherapy will be enrolled.”
- Modifies eligibility criteria to (1) permit baseline neutrophil and platelet counts to be obtained within 14 days (from 7 days) of study entry; (2) require that patients with low-grade NHL that has undergone transformation to a higher grade histology must have been treated with a prior therapy for intermediate-grade lymphoma. Re-biopsy to rule out transformation and to confirm low grade histology will be required only for those patients who have not received appropriate therapy for intermediate-grade lymphoma.
- Monitoring plan specifies thyroid function tests (total T3, free T4, and TSH) and timing of assessment (baseline, week 25, and at follow-up)
- Deletes determination of “best” response rates and comparisons of “best” response rates between Iodine I-131 tositumomab and LQC.
- Interim analysis plan expanded to state that analysis will include data on chemotherapy refractory status and on LQC as assessed by the independent review panel, percent of patients with non-equivalent durations of response following the LQC and Iodine I-131 tositumomab. The percent of patients contributing to the primary endpoint analysis will be calculated. The sample size will be adjusted if the percent suggests that primary endpoints analysis is underpowered.
- Objectives for independent-review panel specified. They are to obtain an independent confirmation of investigator-assessed response to therapy (LQC and Iodine I-131 tositumomab) and to verify the investigator’s assessment of each patient’s chemotherapy refractory status.

Amendment 6 - -----

- Eligibility criteria modified to (1) to state that patients must *objective* evidence of disease progression or failure to respond; (2) requirement for baseline creatinine changed from <2.0 mg/dL to <1.5 times the upper limit of normal (ULN), requirement for baseline bilirubin changed from <2.0 mg/dL to <1.5 x ULN, and new requirement for AST and ALT < 5 times ULN added.

- Addition of CRO for data management responsibilities of independent review panel activities

Amendment 7 – -----

- Modifies endpoints and analytic plan to state that the Independent review panel only reviews the fully assess the comparison of duration of response (primary study endpoint). All efficacy analyses will be performed using the investigator assess and *when appropriate*, the masked, independent review panel-assessed data.
- Study population modified at FDA's request to include all patients who received at least a portion of the dosimetric dose in the primary efficacy analysis. Patients who are HAMA-seropositive will not be replaced and these patients will be included in the efficacy analysis.
- Revision of criteria for "removal from study". Patients with adverse experiences that "require discontinuation of therapy" will not be removed from study.
- Definition of response revised from CR, CCR or PR confirmed by two separate response evaluations at least 4 weeks apart to "best response evaluation (ordered by CR, CCR, PR, SD, then PD) and does not require subsequent confirmation. Adds definition of "confirmed response" that requires CR, CCR or PR be confirmed by two separate response evaluations at least 4 weeks apart
- Modification of definition of "intent-to-treat" population, adding the phrase "including all patients who received at least a portion of the dosimetric dose"
- Appendix titled "Independent Review of Efficacy Data" deleted and replaced with "the Prior contents of the appendix have been superseded by the "Charter for the Independent Review of Efficacy and Chemotherapy-refractory Status in Study RIT-II-004".

Amendment 8 – -----

- Administrative changes reflecting acquisition of Coulter Pharmaceuticals by Corixa Corp.
- Modification to plan for long-term follow-up (LTFU)- plan now requires TSH and HAMA testing every 12 months.
- Modification to informed consent document describing risks of hypothyroidism as a delayed toxicity and of the additional testing requirements for LTFU.

Amendment to the Statistical analysis plan, not identified as a protocol amendment in the BLA ---- -----

- The independent review of data was expanded from the assessment of the primary endpoint to include the assessments of secondary endpoints in study RIT-II-004 ("Expanded MIRROR Panel").

STUDY RESULTS

Patient Disposition

Sixty-one patients were enrolled at 8 centers.

- One patient (004-015-002) was not administered any study drug. The patient was enrolled on Feb. ---, 1997 and withdrew consent. The date of last follow-up for this patient is April 29, 1997.
- 60 patients received the dosimetric dose
 - One patient (004-018-001) received the dosimetric dose; the patient was withdrawn from study for encephalopathy on study day 13 prior to receiving the therapeutic dose.
 - One patient (004-015-005) received the dosimetric dose but experienced an infusion-related adverse experience on the day of the therapeutic dose infusion. The event occurred during administration of the unlabeled tositumomab, resulting in termination of treatment prior to administration of the radiolabeled portion of the therapeutic dose.
- 58 patients received both the dosimetric dose and the therapeutic dose.

Study RIT-II-004: Enrollment by Protocol Amendment

Submission	Submission Date	Cumulative Number of Subjects Enrolled
Original Protocol	-----	4
Amendment 1	-----	21
Amendment 2	-----	22
Amendment 3	-----	26
Amendment 4	-----	53
Amendment 5	-----	58
Amendment 6	-----	61
Amendment 7	-----	61
Amendment 8	-----	61
Total Enrollment		61

Conduct of the Study

FDA's review of the case report forms for study RIT-II-004 noted the following unreported protocol violations of eligibility criteria for Subject No: 004-014-001, 004-018-001 and 004-020-007. These violations were discovered in the course of the review of case report forms.

The subject was enrolled on December ---, 1996. The subject received fludarabine from June 3 through August 2, 1996. CT scan evaluations obtained prior to fludarabine were interpreted by the MIRROR as an SPPD of 66.66 cm². CT scans following fludarabine on Aug 21, 1996 were read with an SPPD of 43.16 cm². Baseline enrollment CT scans on study entry, December---, 1996, were read with an SPPD of 22.00 cm², documenting a decrease in the SPPD of 67%. Thus the subject had a PR to fludarabine at study entry, in violation of the eligibility criteria.

004-018-001: This 39 yo female experienced rapidly progressive disease through prior therapy. Prior treatment included cytarabine 1 gm/m² and etoposide 100 mg/m² IV on days 1-5, administered on October ---, (cycle 1) and November ----, 1996 (cycle 2). The second cycle was complicated by catheter-related sepsis (Staph aureus) treated with catheter removal. CBC, creatinine and liver functions were normal during that admission. The patient was re-admitted for the dosimetric dose on November ---, 1996 (study day – 2) with increasing pleural effusions. Following administration of the dosimetric dose on Nov. ---, 1996 (day 0), she underwent thoracentesis and chest tube placement. On study day 6, the patient was noted to have hyperbilirubinemia and increased LFTs. On Dec. ---

1996 (study day 10), she was admitted for the therapeutic dose with a history of increasing lethargy and 2-3 day history of confusion described as “trouble finding the right words”. Examination reports extensive expressive and receptive dysphasia with slight impairment of memory. The patient was mildly thrombocytopenic (77,000) with worsening LFTs, notably LDH of 11,640 IU/ml. A diagnosis of hepatic encephalopathy was made on study day 12, with progressive hepatic deterioration and death on study day 14.

004-020-007: 45 yo male with diagnosis of NHL in Dec. 1994 and multiple chemotherapeutic regimens prior to study entry, received therapeutic dose of 82 mCi (75 cGy TBD) on Jan --, 1998. Baseline CBC (12/12/97) revealed ANC 5.6, hemoglobin 12 gm/dL, and platelets 116,000. The patient responded to treatment (apparent CR) but suffered persistent thrombocytopenia through 1998 and 1999 with development of leukopenia in 1999 and a diagnosis of **MDS** in September 1999. The patient suffered subdural hematoma in June 2000 (secondary to thrombocytopenia) and died with progressive hemorrhage and hemoptysis on -----.

Subjects for whom protocol violations were identified by the sponsor, are summarized in the following table.

Patent ID	NHL subtype	Dose (cGy)	Study day	Violation type	Description
Violation of Eligibility Criteria					
004-013-004 66F T75C	T	75	0	ENTRY	WBC = 2.9, current protocol required >3.5 but was being amended
004-016-002 80M T65C	T	65	-1	ENTRY	WBC = 3.5, current protocol required >3.5 but was being amended
004-016-009 68M T75L	T	75	-8	ENTRY	Bone marrow involvement based on unilateral biopsy (20-25%)
004-013-017 65M T65L	T	65	0	ENTRY	Patient received oral prednisone 13 days prior to study entry
004-020-002 50M T75C	T	75	0	ENTRY	CT scans 29 days prior to enrollment (protocol requires 28 days)
<u>Violations of Informed Consent</u>					
004-014-006 48M L75L	L	75	-2	ENTRY	Verbal informed consent given, not signed until after enrollment (9/4/97)
004-018-001 39F T00C	T	0	-1	ENTRY	Informed consent not approved by ethics committee when signed

Violation of Eligible NHL Histology

004-021-001 51M I75C	I	75	0	ENTRY	Mantle cell, pathology re-read
<u>Violation of Thyroid Protection Protocol</u>					
004-013-003 43M T65C	T	65	0	TREATMENT	SSKI started on same day as dosimetric dose Pt was started on SSKI plus potassium perchlorate rather than protocol regimen
004-013-004 66F T75C	T	75	0	TREATMENT	SSKI started on same day as dosimetric dose
004-013-005 63M T75L	T	75	0	TREATMENT	SSKI started on same day as dosimetric dose
004-013-006 38F L75L	L	75	0	TREATMENT	SSKI started on same day as dosimetric dose
004-013-007 55M L75L	L	75	0	TREATMENT	SSKI started on same day as dosimetric dose
004-013-009 61M L75L	L	75	0	TREATMENT	SSKI started on same day as dosimetric dose
004-013-012 66F L75L	L	75	0	TREATMENT	SSKI started on same day as dosimetric dose Lugols solution dosed at 5 gtts tid, protocol requires 20 gtts/day
004-020-008 71M L65L	L	65	0	TREATMENT	
<u>Violation of Timing for Dose Assessment or Administration of Therapeutic Dose</u>					
004-021-002 51M L65L	L	65	15	TREATMENT	Therapeutic dose given 15 days after dosimetric dose Second total body count performed on day 1 and third on day 5
004-029-003 39M L75L	L	75	1	TREATMENT	
<u>Violation of Therapeutic Dose Administration</u>					
004-020-005 66M L88L	L	87.8	8	TREATMENT	Calculated dose 104 mCi, actual dose 125 mCi
004-020-006 60M L75L	L	75	8	TREATMENT	Enrolled at 65 cGy, treated at 75 cGy
004-020-007 45M L75L	L	75	14	TREATMENT	Enrolled at 65 cGy, treated at 75 cGy

Financial Disclosure

Under 21 CFR 54, an applicant is required to certify all investigators and consultants have disclosed any financial arrangements that could influence the study outcome.

The following investigators disclosed one or more of the above types of financial arrangements meeting:

- Mark Kaminski, M.D.- Principal Investigator, University of Michigan
- Richard Wahl, M.D. – Principal Investigator, University of Michigan
- Susan Knox, M.D.- Principal Investigator, Stanford University
- David Colcher, Ph. D.- Investigator, University of Nebraska

FDA Assessment of Potential Conflicts- There was no evidence that the data from these sites were significantly different from other study sites or altered the results of the study.

Bioresearch Monitoring Inspection Results

Inspections of five clinical sites were performed in support of BLA 99-0813 for Protocol RIT-II-004 entitled “Multicenter, Pivotal Phase III Study of Iodine-131 Anti-B1 Antibody (Murine) Radioimmunotherapy for Chemotherapy-Refractory Low-Grade B-Cell Lymphomas and Low-Grade Lymphomas that have Transformed to Higher Grade Histologies.” In addition one of the sites (University of Nebraska) was also inspected for Protocol RIT-II-001, entitled “Multicenter, Phase II Dosimetry/Validation Study of 131Iodine-AntiB1(murine) Radioimmunotherapy for Chemotherapy-Refractory Low-Grade B-Cell Lymphomas and Low-Grade Lymphomas that have Transformed to Higher Grades” after the sponsor reported that data was missing. The inspections were conducted in accordance with CPGM 7348.811, the Inspection Program for Clinical Investigators.

Specific questions concerning the studies were included. Data audits were performed at the following five sites:

Site	Investigator	Form 483	Classification
Kaiser - Vallejo	Dr. Fehrenbacher	No	VAI
Stanford University	Dr. Knox	Yes	VAI
University of Michigan	Dr. Kaminski	Yes	VAI
University of Washington	Dr. Press	Yes	VAI
University of Nebraska	Dr. Vose	Yes	VAI

Inspectional Summary Statement

The results of bioresearch monitoring inspections indicate that the deviations are not substantive, with the exceptions noted (verification of dose delivered), and that the submitted data can be considered reliable and accurate.

Study Population:

The study population consists of low grade and follicular NHL; approximately 1/3 of the patients have disease, which has transformed to a higher histologic subtype. The population has been heavily pretreated with chemotherapy (median number of prior regimens —4) but not radiotherapy. None of the patients have undergone dose-intensive chemotherapy with prior stem cell support. The majority had advance disease (stage III and IV) and 11% have bulky lesions. The characteristics of the population at study entry are summarized in the following table.

Baseline Characteristics for Patient Population in Study RIT-II-004

Baseline Characteristic	ITT population n=61
Age (years)	
Median(range)	59 (38-82)
Q1; Q3	52; 68
Gender	
Males (%)	38 (62%)
Race	
Caucasian (%)	59 (97%)
Histologic diagnosis at entry	
W/o transformation	
Low grade	37 (61%)
Intermediate grade	1 (2%)
High grade	0
With transformation	
Low grade	0
Intermediate grade	23 (37%)
High grade	0
Stage of disease	
I	0
II	1 (2%)
III	13 (21%)
IV	47 (77%)
Missing	0
IPI category	
0	0
1	7 (12%)
2	22 (36%)
3	22 (36%)
4	7 (12%)
5	1 (2%)
Missing	2 (3%)
Max. tumor diameter	
< 5 cm	25 (41%)
≥ 5, ≤10 cm	29 (48%)
> 10 cm	7 (11%)
# Prior chemo regimens	
Median (range)	4 (2-13)
25 th , 75 th quartiles	3, 5
# Prior RT regimens	
Median (range)	0 (0-7)
25 th , 75 th quartiles	0, 1
No Prior BMT	61 (100%)
Time from diagnosis to entry (mos)	
Median (range)	4.4 (0.8, 27.8)
25 th , 75 th quartiles	2.6, 7.2

Primary Efficacy Outcome:

The response to treatment and response duration for the most recent qualifying chemotherapy regimen and for Iodine I-131 tositumomab was determined by the Expanded MIRROR panel for 60 patients; data were not reviewed for the patient who withdrew from study and received neither the dosimetric nor therapeutic dose. There were 7 patients who responded to the LQC for an ORR of 12% and a CR/CCR of 2%. There were 28 subjects who responded to Iodine I-131 tositumomab for an ORR of 47% and a CR/CCR of 20%. The response determinations by the MIRROR panel are summarized in the table below.

Treatment Response by Expanded MIRROR Panel (Effoutm dataset) According to Treatment for Patients enrolled in RIT-II-004		
Response Category	Last Qualifying Chemotherapy	IODINE I-131 TOSITUMOMAB
Complete Response	1	8
Complete Clinical Response	0	4
Partial Response	6	16
Stable Disease	5	4
Progressive disease	48	28
Total Patients	60	60

There were 28 patients whose disease did not respond to either therapy or for whom the duration of response to either therapy was roughly equivalent (< 30 days difference in the duration of response to either treatment). This group was classified as "Duration Equivalent".

	Response to Iodine I-131 tositumomab	No Response to Iodine I-131 tositumomab	
Responded to LQC	3	4	7
No Response to LQC	25	28	53
	28	32	

The remaining 32 patients achieved an objective tumor response (CR, CCR, or PR) following Iodine I-131 tositumomab, the last qualifying chemotherapy regimen, with a difference in the durations of response to Iodine I-131 tositumomab and to the last qualifying chemotherapy regimen of more than 30 days. Among these 32 patients, 27 patients experienced a longer duration of response to Iodine I-131 tositumomab (difference in the durations ≥ 30 days) as compared to the duration of response to last qualifying chemotherapy regimen. This group of 27 consisted of 25 patients who failed to respond to the LQC but did respond to Iodine I-131 tositumomab and 2 patients who responded to both the LQC and to Iodine I-131 tositumomab but had a longer duration of

response to Iodine I-131 tositumomab than to LQC (difference in response durations \geq 30 days).

	Response to Iodine I-131 tositumomab	No Response to Iodine I-131 tositumomab	
Responded to LQC	(2 + 1)	4	7
No Response to LQC	25	28	53
	(27 + 1)	32	

The remaining 5 patients experienced a longer duration of response to the last qualifying chemotherapy regimen (difference in the durations \geq 30 days) as compared to the duration of response to Iodine I-131 tositumomab. This group was comprised of 4 patients who responded to the LQC but not to Iodine I-131 tositumomab and one patient who responded to both the LQC and Iodine I-131 tositumomab, in whom the duration of response to LQC was longer than to Iodine I-131 tositumomab.

	Response to Iodine I-131 tositumomab	No Response to Iodine I-131 tositumomab	
Responded to LQC	(2 + 1)	4	7 (2 + 5)
No Response to LQC	25	28	53
	28	32	

Based on the Expanded MIRROR Panel assessment of response and response duration as described above, the following proportions were generated for use in the primary efficacy analysis:

28/60 (47%) patients had an equivalent duration of response

32/60 (53%) patients had a non-equivalent duration of response

- 27/32 (84%) patients had a longer duration of response to Iodine I-131 tositumomab
- 5/32 (16%) patients had a longer duration of response to the last qualifying chemotherapy regimen

Primary Efficacy Analysis

The primary efficacy endpoint of the study was the comparison, as assessed by the Masked Independent Randomized Radiology and Oncology Review (MIRROR) panel, of the number of patients having a longer duration of response (i.e., more than 30 days) on their last qualifying chemotherapy regimen to the number of patients having a longer duration of response on IODINE I-131 TOSITUMOMAB™.

FDA followed the protocol defined primary endpoint and compared the duration of response on I-131 Antibody therapy to prior chemotherapy. The duration of response is linked with the response. If there is no response (SD, PD) on both (Bexaar & Prior Chemo) then these patients were classified as equivalent regardless of how long their Stable Disease (in favor of either Iodine I-131 tositumomab or prior Chemo) was or if they had a response (CR, CCR or PR), but the difference in the duration of response between Bexaar and prior Chemo was less than 30 days. There were 28 patients in this group. The remaining 32 patients had a CR or CCR or PR on either therapy and the difference in the duration of response was more than 30 days. There were 27 patients from these 32 whose the duration of response was longer than 30 days on Iodine I-131 tositumomab as compared to Prior Chemo, and 5 from these 32 whose duration of response was longer than 30 days on prior chemo as compared to Bexaar.

Using this algorithm, the following table provides a summary of the results for the primary endpoint for confirmed responses:

Response	Frequency	% of 60
Equivalent duration	28	47 %
Longer response with Iodine I-131 tositumomab	27	45 %
Longer response with Chemo	5	8 %

The sign-rank test takes all data into account, equivalent as well as non- equivalent cases, and tests the hypothesis that overall there is a statistically change. Then two proportions can be compared.

$p < 0.0001$ using sign-rank test in favor of Bexaar.

Analysis of Proportions

Let p_1 = proportions of equivalent responses

p_2 = proportions of responses favoring Iodine I-131 tositumomab

p_3 = proportions of responses favoring prior chemotherapy

Of interest is to test the null hypothesis $H_0 : p_2 = p_3$ conditioned on equivalent response, i.e., ignoring equivalent response, and n becomes 32, and test is $H_0 : p_2 = p_3 = 0.5$ versus $H_1 : p_2 \neq p_3$. The p-value for testing this H_0 is < 0.0001 (Exact Binomial test) **in favor of Bexaar**

Note: FDA's analysis differs slightly from the analysis of the primary efficacy endpoint as performed by the sponsor.

While, FDA and the sponsor used different approaches to assess the primary endpoint, the results of both tests were similar; both demonstrating a highly significant increase in the durations of response after Iodine I-131 tositumomab. The sponsor applied the one-sided exact McNemar's test for comparing the number of patients with longer response on Iodine I-131 tositumomab compared to the number of patients with longer response on chemotherapy. This test only accounts for patients with nonequivalent durations of response. FDA applied the Wilcoxon signed rank test using all response duration data. As the Wilcoxon signed rank test includes the magnitude of the duration of response, it is more powerful in this study (as the higher response rate after Iodine I-131 tositumomab is also associated with a longer duration of response). The sponsor

approach accounts for the paired censored data. As the censored values were almost exclusively with the longest durations of response, the censoring effect is minimal. Thus, while the statistical approaches used by FDA and the sponsor differed, the conclusions were similar.

Secondary Efficacy Outcomes

1. Comparison of other efficacy outcomes between Iodine I-131 tositumomab and LQC: The protocol identified several secondary endpoints, including comparisons between efficacy outcomes following Iodine I-131 tositumomab as compared to the most recent qualifying chemotherapy regimen. These outcomes included comparisons of overall response rates, complete response rates, durations of overall response and of complete responses. For each of these analyses, the differences were in favor of Iodine I-131 tositumomab and were significantly different.

MIRROR Panel–Assessed Secondary Efficacy Endpoint Data:
Study RIT-II-004 (N = 60)

Secondary Efficacy Endpoints	Last Qualifying Chemotherapy (N = 60)	Iodine I 131 tositumomab (N = 60)
Overall Response Rate	7/60 (12%)	28/60 (47%)
Median (95% CI) duration of response for responders (months)	4.1 (3.0–5.4)	11.7 (6.9–NR)
Complete response Rate	1/60 (2%)	12/60 (20%)
Median (95% CI) duration of response for complete responders (months)	4.8	NR (12.5–NR)

Exploratory Analyses

1. Subset analyses of the primary efficacy analysis in patients whose disease has undergone transformation and in patients whose disease has not undergone transformation to a higher histologic subtype of NHL.

Subset analyses were done comparing Last Qualifying Chemotherapy Response – Original & Expanded MIRROR Assessed to Iodine I-131 tositumomab Confirmed Response – expanded MIRROR Assessed to evaluate if the original and expanded MIRROR assessment made any difference to the efficacy of the primary endpoint for each of the following two subset populations.

- (1) Patients with low grade non-Hodgkin's lymphoma (NHL) that has not undergone transformation (36 patients) – Not Transformed
- (2) Patients with intermediate grade, follicular NHL that has not undergone transformation (1 patient)

- (3) Patients with low grade non-Hodgkin's lymphoma (NHL) that has undergone transformation (23 patients) – Transformed

Last Qualifying Chemotherapy Response Versus Iodine I-131 tositumomab
Confirmed Response – expanded MIRROR Assessed

Using previously defined algorithm, the following table provides a summary of the results of the subset analysis for the primary endpoint (the patient with an intermediate grade histologic subtype of NHL was not classified as not transformed, this patient was a non-responder):

Response	Low Grade/follicular		Transformed	
	Frequency	% of 37	Frequency	% of 23
Equivalent response duration	11	30 %	17	74 %
Longer duration with Iodine I-131 tositumomab	22	59 %	5	22 %
Longer duration with Chemo	4	11 %	1	4 %
p-value (sign-rank test)	<0.0001		0.0625	

Conclusions: There is a significant difference in favor of Iodine I-131 tositumomab for patients with low grade, untransformed NHL ($p < 0.0001$), but not significantly different in patients with NHL with transformation, ($p = 0.0625$, trend in favor of Iodine I-131 tositumomab). Iodine I-131 tositumomab activity is different in two sub-populations. The patients with NHL without transformation (all but one with low grade histologic subtype) benefit significantly more from Iodine I-131 tositumomab than transformed patients ($p = 0.0071$, Fisher's exact test).

2. Assessment of response to Iodine I-131 tositumomab in patient subsets (patients with and without evidence of histologic transformation to a more aggressive (higher grade) histologic subtype).

At the initiation of the study, the sponsor was urged to limit the patient population to a more homogeneous group. Specifically, the sponsor was asked to exclude subjects with evidence of histologic transformation since FDA felt this was a biologically different disease than low grade and follicular lymphoma. The sponsor declined, stating that evidence of histologic transformation was a prognostic factor but only one of many in this chemotherapy refractory population. As a result of these discussions, the protocol was to include a plan for analysis of the study results in patient subsets, i.e., those with and those without evidence of histologic transformation. As can be seen in the table below, the likelihood of achieving a response was much lower in the transformed subset.

Response Category	Response Rate in Subset without Transformation	Response Rates in Subset with Transformation N =23
CR	14% (5/37)	13%(3/23)
CCR	11% (4/37)	0 (0/23)
PR	38% (14/37)	8% (2/23)
ORR	62% (23/37)	21% (5/23)
SD	8% (3/37)	4% (1/23)
PD	30% (11/37)	74% (17/23)

3. Analyses of response according to I-131 dose administered

The dose of 131-Iodine administered was derived for each subject. This exploratory analyses were conducted to assess for relationships between response to Iodine I-131 tositumomab treatment and the total dose of 131-I administered or the dose adjusted for body mass or surface area administered. The results are presented in the table below.

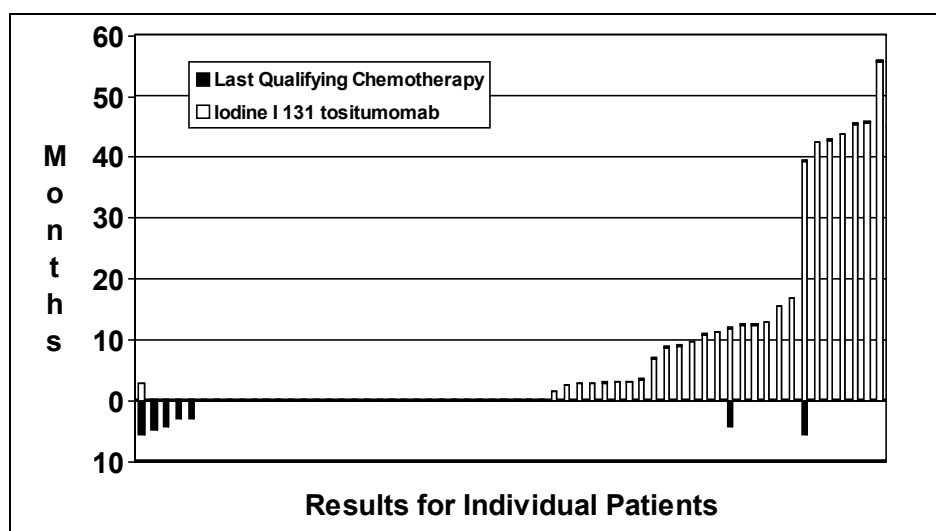
Confirmed Response according to Dose of Iodine-131			
Dose Basis	Non Response	Response	Total
Dose (mCi)			
Median	77.9	97.7	90.2
Range	(0-173.4)	(47.2-212)	(0-212)
Dose (mCi/m²)			
Median	43.9	49.7	46.4
Range	(0-83.8)	(33-100)	(0-100)
Dose (mCi/kg)			
Median	1.1	1.2	1.2
Range	(0-2)	(0.9-2.4)	(0-2.4)

4. During the course of the study, the source of the tositumomab antibody was changed from ----- to Coulter. The antibodies from the different manufacturing sites were biochemically comparable and yielded a similar pharmacokinetic profile. A comparison of the response rates by antibody-source showed a slightly higher but not significantly different response rate for the -----manufactured antibody product than for the Coulter-manufactured product.

I-131-B1 Therapy Response Assessment by Antibody Manufacturer		
Antibody Manufacturer	Overall Response Rate (No. responders/total)	Total number of patients treated
Coulter-manufactured antibody	35% (7/20)	20
-----manufactured antibody	52% (21/40)	40
Total	46% (28/60)	60

The following figure illustrates the relative comparison of the duration of response for each patient following treatment with their LQC and following treatment with iodine I 131 tositumomab. On the left side of the figure are data from 5 patients with a longer duration of response for the LQC; in the center there are data from 29 patients with less than 30 days difference in the duration of response; and on the right side of the figure are data from 26 patients with a longer duration of response after iodine I 131 tositumomab.

Figure: Paired Comparison of Duration of Response



Safety Assessment

The most common and the most severe adverse events were hematologic toxicities. The following are the most common non-hematologic toxicities: asthenia (57%), fever (38%), nausea (37%), increased cough (30%), pain (25%), anorexia (25%), vomiting (22%), diarrhea (22%), abdominal pain (20%), chills (18%), infection (17%), and dyspnea (15%). The non-hematologic toxicities were predominantly mild to moderate in severity. The hematologic toxicities were predominantly severe (grade 3 or 4 according to the NCI CTC) and prolonged in nature. The profile of the hematologic toxicity is summarized in the following table.

Per-Patient Incidence of Grade 3-4 Hematologic Toxicity

Hematologic Toxicity	Efficacy studies n=229
Neutropenia	
% Documented Grade 3-4 toxicity	59%
Median days to nadir (95% CI)	42 (41, 45)
25 th and 75 th percentiles for days to nadir	39 ; 47
Median duration of documented Grade 3-4 toxicity	30 (22, 43)
25 th and 75 th percentiles for duration of toxicity (days)	21; 49
Thrombocytopenia	
% Documented Grade 3-4 toxicity	48%
Median days to nadir (95% CI)	34 (32, 35)
25 th and 75 th percentiles for days to nadir	28; 40
Median duration of documented Grade 3-4 toxicity	29 (23, 40)

25 th and 75 th percentiles for duration of toxicity (days)	22; 43
Anemia	
% Documented Grade 3-4 toxicity	19%
Median days to nadir (95% CI)	48 (42, 55)
25 th and 75 th percentiles for days to nadir	39; 60
Median duration of documented Grade 3-4 toxicity	22 (6, 36)
25 th and 75 th percentiles for duration of toxicity (days)	16; 36

Serious Adverse Events (SAE)

There were 23 SAE reported in 17 (28%) patients. An additional 4 patients (7% of the study population) developed MDS. A summary of these events are provided below

- 004-013-001- 69 yo male who presented with dyspnea, right-sided pleuritic chest pain, dry cough and fatigue on study day 68. The patient was not febrile and ANC was 1.7. A VQ scan was indeterminate. The patient was treated with antibiotics and coumadin (for presumptive diagnoses of **pneumonia** and/or **pulmonary embolism**)
- 004-013-002- 62 yo female hospitalized on study day 75 with productive cough and wheezing. The patient was afebrile and ANC was normal. The patient was treated for **exacerbation of COPD** and **bronchitis**, with symptomatic improvement.
- 004-013-005- 63 yo male developed rapidly progressive disease, particularly a cervical mass with compression of local structures. The patient was removed from study on day 20. On study day 30, he was admitted with fever, non-productive cough, anemia and thrombocytopenia (ANC was grade 0). The presumptive diagnosis was **aspiration pneumonia**. The patient also required platelet and RBC transfusions. He did not respond to antibiotic therapy with persistent fevers and progressive disease. He died on study day 43.
- 004-015-005- 59 yo male who admitted for his therapeutic infusion on study day 8. The infusion was interrupted three times severe Infusional toxicity within 5 minutes of the initiation of infusion on each attempt. The infusion reactions consisted of severe rigors, tachycardia to 133 bpm, and on the last attempt, temperature of 39.4 in conjunction with severe rigors. The patient was observed overnight and remained afebrile. A pre-infusion HAMA was negative; a post-infusion attempt HAMA was not obtained. Although not identified as an SAE, this would appear to represent a significant **allergic reaction** requiring in-patient observation. The patient never received the radiolabeled portion of the therapeutic dose. The patient was subsequently hospitalized on study day 20 for **pneumonia**. The patient was hospitalized on study day 91 for a second episode of **pneumonia** and anemia requiring 5 units pRBCs (discharged with hemoglobin on 8.5 gmn/dL). The patient had evidence of persistent anemia and received additional pRBC transfusions and a course of epoietin therapy (study days 111-181). The patient had several subsequent admissions for bronchitis and pneumonia prior to removal from study on day 168 for disease progression.
- 004-013-010: 53 yo male developed shaking chills and fever to 39.1 C the evening of the dosimetric dose infusion. The fever and chills resolved. The patient was admitted for the therapeutic dose and again experience fever and shaking chills that evening. The patient was subsequently diagnosed with **catheter-related sepsis** on study day 16 after continued fevers and development of tenderness at the port-a-cath site. The patient was admitted for catheter removal on study day 23 and was noted to be hypoxic. A diagnosis of **P. carinii pneumonia** was made and he was

treated with antibiotics including high dose Bactrim. On study day 42, the patient developed pancytopenia, requiring transfusions, filgrastim, and dose-reduction of Bactrim; cytopenias recovered by study day 62.

- 004-013-013: 55 yo female who was diagnosed with superior vena cava syndrome secondary to thrombosis (attributed to catheter) on study day 28
- 004-013-017: 62 yo male admitted on study day 21 for **abdominal distention, constipation, and left sided chest pain**. The etiology of these complaints remains unclear. The patient was also admitted on study day 47 for **anemia** requiring transfusions (intermittently until patient left study on day 60) and on study day 56 for thoracentesis. The patient was withdrawn from study on day 57 for progression disease.
- 004-014-002: 58 yo female admitted on study day 13 and 22 for **severe pain, pitting edema of the extremities due to disease progression**. The patient **died** of progressive disease on day 41.
- 004-014-007: 58 yo female who was removed from study on day 24 for disease progression and **died** on study day 79
- 004-015-003: 59 yo male was hospitalized for therapeutic dose administered on study day 9 and developed new onset **atrial flutter** on study day 12. Patient under successful conversion to normal sinus rhythm on study day
- 004-015-006: 71 yo female fell on study day 77 and **fractured her right hip**. Post-operative course complicated by persistent fevers and confusion. Patient was discharged from study on day 110 due to the intervening medical complications and died at home on study day 136.
- 004-106-001: 62 yo male with normal platelet count of 160,000, ANC 2.5 and hemoglobin on study day 0. On the day of therapeutic infusion, platelet count was 140,000. Patient was dosed at 75mCi TBD based on day 0 CBC. The patient experience transient cytopenias days 34-42. On study day 131, patient was admitted with **febrile neutropenia** and **pancytopenia**. Subsequent course complicated by H. simplex infection. The patient was treated with filgrastim and transfusion support. Recovery of counts was documented on study day 167.
- 004-016-003: 45 yo female with multiple chemotherapeutic regimens prior to entry, received 75cGy TBD in May 1997. The patient had an ongoing CR as of September 1999 with normal CBC, however cytogenetics were abnormal on bone marrow aspirate in Oct. 1999. Patient has had repeated abnormal cytogenetics with normal CBC as of August 2000. This patient has a diagnosis of evolving **MDS**.
- 004-016-004: 55 yo male admitted on study day 73 with **intractable nausea and vomiting, dehydration and renal failure**. The patient was removed from study on day 77. The etiology of the protracted vomiting was felt to be due to disease progression and the patient subsequently received additional chemotherapy.
- 004-016-007: 61 yo male with multiple prior chemotherapeutic regimens who received 75 cGy TBD in August 1997. The patient was platelet and RBC transfusions intermittently between September and December 1997. The patient had persistent thrombocytopenia (45,000-78,000) throughout 1998 and 1999. Although disease progression was documented in 1998, he received no additional treatment for NHL. A diagnosis of **MDS** was made in Jan. 2001.
- 004-016-008: 72 yo female presented with **worsening of pre-existing peripheral neuropathy** (burning leg pain bilaterally) on study day 20. Symptoms persisted and worsened despite outpatient medical management in a pain clinic. The patient was admitted on study day 74 with intractable pain from arthralgias, myalgias, and neuropathy. Management during hospitalization not well described; the patient was

discharged on study day 81 on gabapentin with improvement in pain. Pain was persistent at study day 188.

- 004-016-011: 75 yo female with a history of prior SVT (on therapeutic anticoagulation) and a history of dyspnea on exertion on study day -1. The patient continued to have dyspnea, which progressed over time and was attributed to disease progression (including chest wall mass and recurrent pleural effusion) following treatment. The patient was hospitalized on study day 52 for **increasing dyspnea** attributed the chest wall mass causing restriction, and to a lesser degree, recurrent pleural. Although "cardiomegaly" is reported by sponsor, narrative summary states that LVEF was normal and heart was normal size. The patient was discharged to hospice and died on study day 61.
- 004-018-001: This 39 yo female experienced rapidly progressive disease through prior therapy. Prior treatment included cytarabine 1 gm/m² and etoposide 100 mg/m² IV on days 1-5, administered on October ---, (cycle 1) and November ----, 1996 (cycle 2). The second cycle was complicated by catheter-related sepsis (Staph aureus) treated with catheter removal. CBC, creatinine and liver functions were normal during that admission. The patient was re-admitted for the dosimetric dose on November ---, 1996 (study day -2) with increasing pleural effusions. Following administration of the dosimetric dose on Nov. ---, 1996 (day 0), she underwent thoracentesis and chest tube placement. On study day 6, the patient was noted to have hyperbilirubinemia and increased LFTs. On Dec. --- 1996 (study day 10), she was admitted for the therapeutic dose with a history of increasing lethargy and 2-3 day history of confusion described as "trouble finding the right words". Examination reports extensive expressive and receptive dysphasia with slight impairment of memory. The patient was mildly thrombocytopenic (77,000) with worsening LFTs, notably LDH of 11,640 IU/ml. A diagnosis of hepatic encephalopathy was made on study day 12, with progressive hepatic deterioration and death on study day 14.
- 004-020-007: 45 yo male with diagnosis of NHL in Dec. 1994 and multiple chemotherapeutic regimens prior to study entry, received therapeutic dose of 82 mCi (75 cGy TBD) on Jan ---, 1998. Baseline CBC (12/12/97) revealed ANC 5.6, hemoglobin 12 gm/dL, and platelets 116,000. The patient responded to treatment (apparent CR) but suffered persistent thrombocytopenia through 1998 and 1999 with development of leukopenia in 1999 and a diagnosis of **MDS** in September 1999. The patient suffered subdural hematoma in June 2000 (secondary to thrombocytopenia) and died with progressive hemorrhage and hemoptysis on -----.
- 004-020-008: 62 yo male with a diagnosis of NHL in November 1995. He received multiple chemotherapeutic regimens prior to study entry in Jan. --, 1998. The patient received the therapeutic dose of 96 mCi (65 cGy TBD) on Jan --, 1998. Pretreatment CBC revealed ANC 1.8 hemoglobin 10.8 and platelet count of 104,000. The most recent prior chemotherapy regimen was CHOP/CNPP which was discontinued on Dec. 11, 1996. The patient achieved a PR to 131-Iodine tositumomab but progressed on study day 392. Subsequent therapy included a single course (4 weekly doses) of Rituxan. The patient's CBC was reported to be "normal" in June 2000, but abnormal in November 2000. A diagnosis of **MDS** was made in Jan. 2001.
- 004-029-001: 72 yo male enrolled on Jan ---, 1998 with a ANC of 2.8, hemoglobin of 16.0 gm/dL, and platelets 134,000 (most recent chemotherapy completed August 1997). The patient received the dosimetric dose on Jan ---, 1998 and a therapeutic dose of 66 mCi (65 cGy TBD) on January ---, 1998. The patient was hospitalized for anuria on study day 85 due to **bilateral obstructive hydronephrosis**, treated with

percutaneous nephrostomy. He simultaneously developed bilateral lower extremity edema; in the evaluation of this, a diagnosis of **bilateral DVT** was made. On study day 90, the patient underwent cystoscopy (reason not provided) and a diagnosis of lymphoma invading the bladder was made.